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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,362	06/23/2006	Martine Petronella Bos	VB60639	1853

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EXAMINER	
GANGLE, BRIAN J	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
11/03/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/584,362	BOS ET AL.	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *1-47,53,54 and 59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-52 and 55-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 June 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/23/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and remarks filed on 7/18/2008 are acknowledged. Claims 45 and 48 are amended.

Election/Restrictions

Applicant's election with traverse of Group IV, claims 48-52 and 55-58, in the reply filed on 7/18/2008 is acknowledged. The traversal is on the ground(s) that Berthet sought to express OstA protein in their vaccines, not downregulate OstA/Imp protein, whereas applicant's invention relates to (a) a gram negative bacterium in which a protein, such as Imp and MsbA, is downregulated, (b) a mutated Imp or MsbA protein, for example, a chimeric protein, (c) polynucleotides comprising a sequence encoding the mutated or chimeric protein of the invention, (d) outer membrane vesicles derived from the gram negative bacteria, (e) methods for producing the chimeric protein or outer membrane vesicle, and (f) methods for the treatment or prevention of gram negative bacterial infection; therefore, Groups I-X have a special technical feature that define a contribution over Berthet.

This is not found persuasive because, despite applicant's assertion, there is no special technical feature linking the claims. Applicant has listed six items which supposedly show a special technical feature. However, the only thing linking the items listed by applicant is a chimeric protein comprising at least one part derived from a Neisserial Imp protein and at least one part from another protein. As set forth previously, that is precisely what Berthet discloses. Therefore, there is no special technical feature linking the claims.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-59 are pending. Claims 1-47, 53-54, and 59 are withdrawn as being drawn to nonelected inventions. Claims 48-52 and 55-58 are currently under examination.

Priority

This application is a 371 of PCT/EP04/14770, filed on 12/21/2004, and claims the benefit of foreign applications 0329827.0 (filed 12/23/2003) and 0416398.6 (filed on 7/22/2004), both

filed in the United Kingdom. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

The information disclosure statement filed on 6/23/2006 has been considered. An initialed copy is enclosed.

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: Figures 2A-2D. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

This application fails to comply with the requirements of 37 C.F.R. 1.821-1.825 because it contains amino acid or nucleotide sequences that are not identified. For example, pages 7, 14, 46, 48, 61, 62, and Figure 8 contain sequences that are not identified. Appropriate sequence identifiers should be used to comply with sequence rules. The sequences in the specification should match the sequence listing and computer readable form (CRF) submitted with the application. Applicant is asked to review the specification for sequences that are not identified and correction is required. Applicant must provide a substitute computer readable form (CRF)

copy of the "Sequence Listing", a substitute paper copy of the "Sequence Listing", an amendment of the specification to insert appropriate sequence identifiers, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

It is noted that the cited occurrences of improper use are only exemplary and applicant should review the specification to correct any other sequence issues.

The use of the trademark TWEEN has been noted in this application on page 30. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

It is noted that the cited occurrence of improper use is only exemplary and applicant should review the specification to correct any other improper use of trademarks.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on pages 6, 41, and 69. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

It is noted that the cited occurrences of improper use are only exemplary and applicant should review the specification to correct any other use of embedded hyperlink and/or other form of browser-executable code.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 56 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claim is drawn to a vaccine comprising an outer membrane vesicle preparation from a Neisserial bacterium that expresses Imp protein, wherein expression of the Imp protein is functionally downregulated by disrupting the structure of the Imp protein such that the level of lipopolysaccharide in the outer membrane is decreased compared to a wild-type Neisserial bacterium, wherein loop 8 of the Imp protein is disrupted by insertion of a part of a Neisserial Hsf protein.

Breadth of the claims: The claims encompass vaccines against all gram negative bacterial infections as well as against neisserial diseases including meningitis (caused by *Neisseria meningitidis*), gonorrhea (caused by *Neisseria gonorrhoeae*), and opportunistic infections caused by other species within the genus.

Guidance of the specification/The existence of working examples: The specification

refers to VA-MENGOC-BC, which is a previously disclosed outer membrane vesicle vaccine that is somewhat effective against serogroups B and C of *Neisseria meningitidis*. The specification does not contain any examples where the claimed outer membrane vesicle vaccine was produced and does not disclose any challenge experiments with any outer membrane compositions to show prevention of any neisserial disease.

State of the art: As stated above, there is an outer membrane vesicle vaccine, VA-MENGOC-BC, that is known in the art. However, there is no guidance in the art with regard to the instantly claimed vaccine or the immunogenicity of outer membrane vesicles containing altered Imp protein. While the skill in the art of immunology is high, to date, prediction of a specific immune response for any given composition in any given animal is quite unpredictable. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie *et al.* (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoepitopes. Bowie *et al.* further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie *et al.* further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Additionally, as evidenced by Greenspan *et al.* (Nature Biotechnology, 7:936-937, 1999), defining epitopes is not as easy as it seems. Greenspan *et al.* recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan *et al.*, an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of

such a residue might profoundly affect binding. As taught in basic immunology texts, an epitope or antigenic determinant interacts with its corresponding antibody based on the three-dimensional structure of both molecules and the fit between them (Cruse *et al.*, Illustrated Dict. of Immunology, 2nd ed., CRC Press, 2003, page 46). These epitopes can be conformational (or discontinuous) epitopes which are formed from separate regions in the primary sequence that are brought together by proper protein folding. Antibodies which bind to conformational epitopes will only bind to proteins folded into their proper native state (Cruse *et al.*, page 166). There are also linear epitopes, which are regions of six amino acids in the primary sequence of a protein. These are generally not found on the surface of a folded protein and are only available to antibodies upon denaturation of a protein (Cruse *et al.*, page 382). Since the instant claims involve methods of inducing a protective immune response specific for an organism, not antibodies specific for a particular linear protein, said antibodies must bind to a protein that is in the proper folded state and which is found on the surface of the organism, and therefore must bind to a conformational epitope. Since a conformational epitope is only found in a properly folded protein and can contain discontinuous portions of the protein, there is no way that one could determine whether a given polypeptide would bind to the antibody unless this were empirically tested. Any change (including deletions and substitutions), anywhere along the polypeptide is likely to alter the three-dimensional structure and folding of the protein, thus altering the antibody-antigen interaction. This is further supported by other authors such as McGuinness *et al.* (Mol. Microbiol., 7:505-514, 1993) and Moudallal *et al.* (EMBO Journal, 1:1005-1010, 1982), who have shown that amino acid deletions, even outside an epitope will alter protein conformation and change antibody-antigen binding. The sum of the art (both old and new) shows that with regard to generating a particular antibody response, the effects of alterations in the sequence of proteins is entirely unpredictable.

Accordingly, it follows that the immunoepitopes that can elicit a particular immune response to a given pathogen can only be identified empirically. This constitutes undue experimentation.

Furthermore, there is no evidence in the art that a vaccine containing antigens from *Neisseria meningitidis* would have any effect whatsoever on diseases caused by other bacteria in general or in the genus *Neisseria*.

Therefore, in view of the lack of support in the art and specification for the claimed vaccine, it would require undue experimentation on the part of the skilled artisan to make and use the vaccine as claimed; thus the claim is not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 48-52 and 55-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 48 is rendered vague and indefinite by the recitation of "Imp protein" and "Neisserial Hsf protein." It is not clear what protein is referred to. While abbreviations are permissible shorthand in the claims, the first recitation should include the full protein name followed by the acronym in parentheses. This rejection affects dependent claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571)272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Brian J Gangle/
Examiner, Art Unit 1645

/Robert B Mondesi/
Supervisory Patent Examiner, Art Unit 1645